REMARKS

Claims 1-3 and 9-11 are currently pending.

I. Section 103 Rejection

A. Rejection of Claims 1 and 9

The Office rejected claims 1 and 9 under 35 U.S.C. §103(a) as being unpatentable over Jain et al., *Brain Research*, Vol. 909, pp. 170-178 (2001) (the "Jain Reference") in view of Cardenas et al., *Arch. Phys. Med. Rehabil.*, Vol. 83, pp. 1708-1714 (Dec. 2002) (the "Cardenas Reference"). Specifically, the Office has asserted that:

> Jain et al. teach that sildenafil is a cGMP PDE5 inhibitor that is useful in the treatment of pain, in particular peripheral antinociception (see in particular results and figures).
>
> Jain et al. does not specifically teach that sildenafil or cGMP PDE5 inhibitors treat somatic pain in a patient suffering from spinal cord injury.
>
> Cardenas et al. teach that chronic pain is associated with spinal cord injury (see whole document). Types of pain include musculoskeletal pain which is a type of somatic pain (see first paragraph on page 1708). Further, spasticity is associated with the musculoskeletal system in which muscles are continuously contracted and causes pain.
>
> It is therefore obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Jain et al., which teach that sildenafil is a cGMP PDE5 inhibitor and is useful in the treatment of peripheral pain, of which somatic pain is part of peripheral pain because it is not associated with the central nervous system, with Cardenas et al. which teach that pain is associated with spinal cord injury. One having ordinary skill in the art at the time the invention was made would be motivated to combine the teachings of Jain et al., with Cardenas et al. because the prior art teaches that sildenafil treats peripheral or somatic pain and spinal cord injury is associated with pain.

Claim 1 specifies a "method for alleviating pain in a patient suffering from spinal cord injury" and claim 9 specifies a "method for alleviating spasticity in patient suffering from spinal cord injury. The Office has expressly acknowledged that the Jain Reference "does not specifically teach that sildenafil or cGMP PDE5 inhibitors treat somatic pain in a patient suffering from spinal cord injury." In fact, the Jain Reference does not specifically teach that sildenafil or cGMP PDE5 inhibitors can be used to treat any type

of spinal cord injury pain. The Jain Reference instead reports the results of a study involving the administration of sildenafil to either a mouse or a rat in four *in vivo* models of nociceptive pain: an acetic acid-induced writhing model, a carrageenan-induced hyperalgesia model, a tail-flick test (radiant heat-induced nociception) model, and a hot-plate test (thermal heat-induced nociception) model. None of these models are models of spinal cord injury pain. Further, although the Jain Reference reports that administration of sildenafil reduced peripheral nociceptive pain in the acetic acid-induced writhing model and the carrageenan-induced hyperalgesia model, it further reports that administration of sildenafil did not impact central nociceptive pain in any of the animal models tested:

> The present study was aimed at exploring the role of the NO–cGMP pathway in nociceptive conditions in experimental animals. Peripheral nociception was assessed by acetic acid-induced chemonociception or carrageenan-induced hyperalgesia and central nociception was assessed by tail-flick and hot-plate methods. Sildenafil exhibited dose-dependent (1, 2, 5 and 10 mg/ kg, i.p.) antinociception in both male and female mice against acetic acid-induced writhing. **However, it did not alter the pain threshold in central nociception (5 and 10 mg/ kg, i.p.).**

The Jain Reference, Abstract, page 170 (emphasis added). The specific results of tail-flick test and hot-plate test used to evaluate the central nociceptive pain threshold are reported in Figure 3 at page 173 of the Jain Reference.

The deficiencies of the Jain Reference are not cured by the Cardenas Reference. The Cardenas Reference characterizes spinal cord injury pain as neurologic pain (generally considered to be associated with the central nervous system) and not musculoskeletal pain (generally associated with peripheral pain):

> The classification system we propose has 2 major categories: neurologic and musculoskeletal. **Neurologic pain is divided into 4 subcategories: SCI pain**, transition zone pain, radicular pain and visceral pain. Musculoskeletal pain is divided into mechanical spine pain (pain in the back or neck affected by activity and position) and overuse pain (often above the injury level in areas of normal injuries or sometimes below the injury level in incomplete injuries).

The Cardenas Reference, page 1709 (emphasis added). Based on the teaching of the Cardenas Reference, one would consider pain and spasticity associated with spinal

cord injury to fall within the neurologic pain category and not the muscloskeletal pain category (i.e., spinal cord injury pain and spasticity are not associated with musculoskeletal tissues) and prescribe treatment for such pain accordingly. The Office has specifically acknowledged that "musculoskeletal pain . . . is a type of somatic pain" and that "somatic pain is part of peripheral pain because it is not associated with the central nervous system." As previously noted above, however, the Jain Reference simply contains no disclosure suggesting that sildenafil or other cGMP PDE5 inhibitors can be used to treat central pain (neurologic or otherwise) generally or spinal cord injury pain specifically. In fact, the Jain Reference reports that sildenafil was ineffective in treating central pain and, therefore, teaches away from using sildenafil to treat spinal cord injury pain.

The specific example presented at pages 17-18 of the application further supports the conclusion that the claimed subject matter is not obvious. This example reports that spinal cord injury Patients 1, 2 and 3 each were "constantly suffering from" limb pain and that Patient 3 was "constantly suffering from" spasticity. One of ordinary skill in the art generally would consider chronic spinal cord injury pain to be neurologic pain requiring centrally directed treatment. The alleviation of such chronic pain and spasticity by administering sildenafil to these patients as described in the application is an unexpected result in view of the disclosure of the Jain Reference that sildenafil has no effect on central pain thresholds and the disclosure of the Cardenas Reference that pain associated with spinal cord injury falls within the neurologic pain category and not the musculoskeletal pain category.

Accordingly, claims 1 and 9 are not obvious based on the Jain Reference in view of the Cardenas Reference.

B. Rejection of Claims 2-3 and 10-11

The Office rejected claims 2-3 and 10-11 under 35 U.S.C. 103(a) as being unpatentable over the Jain Reference in view of the "Cardenas Reference, and further

in view of Maw et al., U.S. Patent 6,856,439 (the "Maw Reference"). Specifically, the Office has asserted that:

> Jain et al. and Cardenas et al. teach that sildenafil treats somatic pain and that pain is associated with spinal cord injury.
>
> Jain et al. and Cardenas et al. do not teach the route of administration or the dosage of sildenafil.
>
> Maw et al. teach a pharmaceutically active compound comprised of a cGMP PDE5 inhibitor that is used to treat various disorders, including female sexual pain disorder and sexual dysfunction due to spinal cord injury (Col. 25, lines 13-20). They further teach that the compound will be administered orally (encompassing claim 2, Col. 25, lines 52-53) and a dose range of tablets as being between 0.01 mg and 500 mg (encompassing claim 3; Col. 27, lines 30-31).
>
> It is therefore obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Jain et al., which teach that sildenafil is a cGMP PDE5 inhibitor and Cardenas et al. which teach that spinal cord injury is associated with pain, with the teachings of Maw et al. which teach a composition comprised of a cGMP PDE5 inhibitor to treat various disorders, including female sexual pain disorder and sexual dysfunction in patients suffering from spinal cord injury. One having ordinary skill in the art at the time the invention was made would be motivated to combine the teachings of Jain et al. and Cardenas et al. with Maw et al. to obtain an efficacious compound to alleviate pain associated with spinal cord injury.

Claims 2 and 3 depend from, and incorporate the requirements of, claim 1. Claims 10 and 11 depend from, and incorporate the requirements of, claim 9. For the same reasons discussed above with respect to the rejections of claims 1 and 9, claims 2, 3, 10 and 11 likewise are not obvious based on the Jain Reference in view of the Cardenas Reference. Combining the teachings of the Jain Reference and the Cardenas Reference with the teachings of the Maw Reference does not alter this conclusion. Although the Maw Reference reports that the claimed cGMP PDE5 inhibitors can be formulated as a pharmaceutical composition for administration to treat various disorders, the underlying deficiencies of the Jain Reference and the Cardenas Reference when relied upon as a basis for the 103(a) rejection remain.

Accordingly, claims 2, 3, 10, and 11 are not obvious based on the Jain Reference in view of the Cardenas Reference and the Maw Patent.

Applicants respectfully submit that the present application is in condition for allowance. To advance the prosecution of the present application, however, the Office is invited to contact the undersigned at the telephone number provided below. If any additional fees are required or an overpayment of fees is made, however, the Office is authorized to debit or credit our Deposit Account No. 16-1445, as necessary.

Respectfully submitted,

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